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HORMESIS FOR FINE PARTICULATE MATTER (PM 2.5)

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□ The hypothesis of hormesis – that substances that harm health at high exposures can reduce risks below background at low exposures, e.g., if they activate defenses without overwhelming them – becomes important for practical policy making if it holds for regulated substances. Recently, the U.S. EPA concluded that reductions in ambient concentrations of fine particulate matter (PM2.5) in air caused trillions of dollars worth of human health benefits for a compliance cost of only about $65 billion per year. This conclusion depends on an unverified assumption of a positive, causal, straight-line relation between PM2.5 concentrations and mortality risks. We review empirical data on PM2.5 and mortality risks (and their precursors, inflammatory responses) and conclude that the PM2.5 concentration-response relation may be J-shaped, rather than linear. This possibility implies that the 1990 Clean Air Act Amendment may well have produced no (or negative) human health benefits, rather than the trillions of dollars worth of reduced mortalities ascribed to it by EPA; and that attempts to achieve further risk-reduction benefits by further reducing PM2.5 concentrations may be counterproductive. This creates a very high value for scientific information that better reveals the true shape of the PM2.5 concentration-response function at and below current ambient levels.

Key words: PM2.5, hormesis, Clean Air Act, air pollution health effects, uncertainty analysis, risk-cost-benefit analysis, Weibull uncertainty distribution

INTRODUCTION

A strong form of the hypothesis of hormesis in toxicology and disease biology states that exposures to sufficiently small concentrations or exposure rates of agents that cause harm at higher levels are typically beneficial, reducing rates of disease or adverse effects below their background levels. A commonly postulated and observed general mechanism for hormesis is that low levels of exposure activate defensive mechanisms without overwhelming them, while higher levels saturate, deplete, or down-regulate the defenses, causing injury. For example, studies of the etiology of lung injury and diseases resulting from exposures to particulates in air have shown that high, prolonged exposures to a variety of particulates induce a non-specific inflammatory response, characterized by an increase in production of reactive oxygen species (ROS) by alveolar macrophages and other lung cells (Janssen *et al.* 1992, Comhair and Erzurum 2002, Azad *et al.* 2008). Low levels of exposure stimulate a compensating production of antioxidants (Janssen *et al.* 1992, Comhair and

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Erzurum 2002) that may compensate – or, if hormesis is correct, more than compensate – for increased ROS production, but experiments in rats show that higher levels of exposure overwhelm and down-regulate this limited defensive capacity, shifting the balance of oxidants and antioxidants toward an abnormally high-ROS environment that may then increase the risks of a variety of lung diseases, from emphysema to lung cancer (Azad *et al.* 2008). Such a mechanistic account naturally suggests that the concentration-response (C-R) function for particulate matter (PM) may have an effective threshold, or a hormetic (U-shaped or J-shaped) shape with a nadir, below which further reductions in exposure concentration, C, do not produce further reductions (and may even increase) the rates of adverse health responses, R.

If the hypothesis of hormesis is to play an important role in informing and improving national science-policy decisions about risk management of low-concentration exposures, it must be evaluated in the context of important real-world risk assessments and risk management decisions. A recent assessment by the United States Environmental Protection Agency (EPA) concluded that further reductions in fine particulate matter (PM2.5) in air are certain to produce further reductions in mortality risks (EPA, 2011) – more specifically, by an amount described by a Weibull uncertainty distribution, which puts zero probability mass on zero and negative values for the slope of the concentration-response relation at low exposure concentrations. This assessment provides an ideal opportunity to examine the plausibility of hormesis for PM2.5. EPA's analysis assumes that the C-R relation between PM2.5 concentrations (C) and mortality risks (R) is well described at low (e.g., present and future) ambient exposure levels by a straight-line, no-threshold function all the way down to the lowest measurable levels. According to this assumption, the C-R relation can be characterized by a single number, the slope of this line, called the C-R coefficient. EPA's uncertainty analysis puts a subjective probability of 100% on positive values for the C-R coefficient, implying that hormesis has zero probability of correctly describing the C-R function for PM2.5. The purpose of this paper is to re-examine this assumption in light of available data, and to re-evaluate whether hormesis might after all give a correct description of the PM2.5 C-R data.

If hormesis turns out to provide a correct description, or even a plausible possibility, for PM2.5, it has crucially important policy implications. Instead of accepting EPA's assumption that further reductions in PM2.5 concentrations will necessarily produce (proportionate) reductions in mortality risks and gains in life expectancy, hormesis would imply that there is an optimal exposure level (which we might have already passed) below which further reductions in PM2.5 concentrations produce no additional gains in public health – let alone the trillions of dollars of health benefits per year projected by EPA. Indeed, at sufficiently low

ambient concentrations, further reductions in PM2.5 could even be associated with modest increases in mortality rates, implying a negative C-R relation. This would require rethinking the wisdom and prudence of continuing to spend resources (estimated by EPA as about $65 billion per year in compliance costs) to reduce PM2.5 concentrations in order to seek hypothesized health benefits that may only become more remote as they are pursued.

META-ANALYSIS OF PM2.5-MORTALITY STUDIES SHOWS BOTH POSITIVE AND NEGATIVE ASSOCIATIONS, SUGGESTING A POSSIBLE J-SHAPED RELATION

Over 100 epidemiological studies have now estimated the concentration-response (C-R) coefficient in regression models of all-cause and cause-specific mortality rates regressed against ambient PM2.5 concentrations and other covariates. A puzzling feature of these studies has been that a sizable minority of them report statistically significant *negative* C-R coefficients, i.e., higher concentrations of PM2.5 are associated with significantly lower mortality rates, even though more report statistically significant positive coefficients. Nearly a decade ago, Dominici *et al.* (2002) found 20 non-significant negative C-R coefficients among 88 cities, although most coefficients in that study (positive and negative) were not statistically significant, due to limitations in sample sizes. Thus, the negative coefficients might have been due to sampling error. However, a more recent review (Franklin *et al.* 2007) found negative C-R coefficients for all-cause mortality and PM2.5 in one third (9 of 27) U.S. communities, with several being statistically significant (including Birmingham, Dallas, and Houston). Although it has been common practice to simply pool results across locations, and to conclude that the pooled mean C-R coefficient is significantly positive (since the 2/3 majority of positive coefficients outweighs the 1/3 of negative ones), this does not resolve the puzzle of why so many locations report negative coefficients.

If the statistical models being used are even approximately correct, then finding multiple statistically significant negative coefficients among 27 locations suggests that negative associations between PM2.5 and mortality rates really do occur. The same logic suggests that the multiple significant positive coefficients are also real. To reconcile these opposing conclusions, it is natural to assume that they are two parts of a larger, non-monotonic relation, e.g., a J-shaped or U-shaped function, with ascending and descending segments. In this case, locations with a high proportion of exposures on the descending part of the C-R relation will have negative average C-R coefficients, while locations with a high proportion of exposures on the ascending portion will have positive average C-R coefficients. Averaging the C-R coefficients across locations is not sensible, however, if the response to changes in concentrations is highly location-spe-

cific – as, indeed, appears to be the case. For example, an examination of C-R curves (rather than assumed constant C-R slope coefficients) for PM10 data in the twenty largest U.S. cities identified U-shaped curves in some cities, although this information was lost when the curved were averaged across cities (Daniels *et al.* 2000).

EPIDEMIOLOGICAL DATA ARE AMBIGUOUS, BUT NOT INCONSISTENT WITH HORMESIS

Evidence for negative, as well as positive, association between PM2.5 concentrations and mortality rates also arises from analyses that take into account model uncertainty by considering *multiple plausible models*, rather than selecting any single model (which would almost certainly be incorrect, given the large number of alternative statistical models that fit the data approximately equally well). Bayesian Model-Averaging (BMA) is one of the best-developed of such "ensemble" methods for using multiple models to reduce model-selection biases and to make more accurate risk predictions and uncertainty characterizations than any single regression model is likely to achieve. Applied to data from 11 Canadian cities, BMA indicates that both total suspended particulate (TSP) and ozone have statistically significant *negative* associations with mortality rates (Koop *et al.* 2007). Similar findings of negative associations for ozone have been reported in the United States (Joseph 2008).

To independently check the validity of such previously published reports of negative C-R relations, one may examine the iHAPSS (internet-based Health and Air Pollution Surveillance System) data base of pollutant levels and mortality rates for U.S. cities made available on-line by Johns Hopkins at www.ihapss.jhsph.edu/. Figure 1 shows plots of cause-specific mortality rate vs. deciles of estimated PM2.5 concentrations. (The data are reconstructed from preprocessed NMMAPS data posted at the website, which documents the smoothing procedure used to preprocess the raw data and the resulting possibility of negative values when data are reconstructed by adding back the smoothed mean. The NMMAPS documentation defines all-cause mortality (*death*) as excluding accidents.) The plots pool data across time (daily data from 1987 to 2000, although different cities started reporting in different years) and across the ten largest metropolitan area in the data base (Chicago, Dallas/Fortworth, Detroit, Houston, LA, Miami, New York, Phoenix, San Diego, and Santa Ana/Anaheim.)

The plots do not suggest any significant positive relations between PM2.5 and excess mortality risk at the lowest exposure concentrations (except possibly for COPD, which is a relatively small contributor to death rates); if anything, they are consistent with a weak negative or U-shaped association between exposures and cause-specific mortality risks for cardiovascular disease (CVD) and pneumonia/influenza mortality risks at the

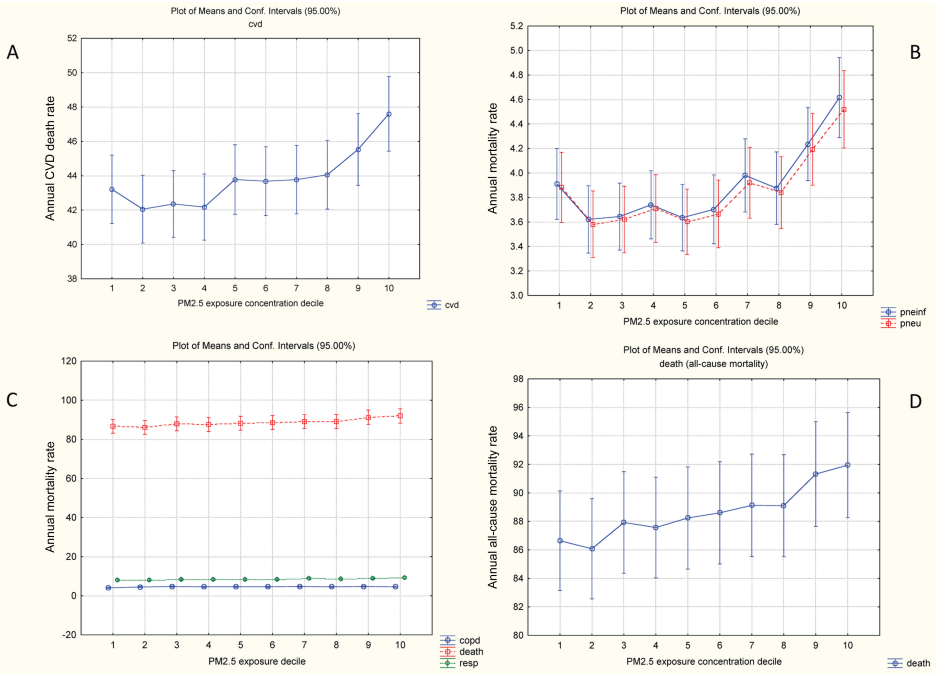


FIGURE 1. PM2.5 and Mortality Rate C-R Relations in Ten U.S. Cities. C-R relations for annual mortality rates: A = cardiovascular disease (CVD); B = pneumonia (pne) and pneumonia/influenza (pneuinf); C = all-case (death), chronic obstructive pulmonary disease (COPD), and respiratory (resp); D = all-cause mortality (expanded from C).

low (left) end of the PM2.5 exposure concentration distribution. The highest (right-most) deciles of the PM2.5 exposure concentration distribution do show increased risks, but it would be inappropriate to extrapolate these linearly down to zero, given the U-shapes of the empirical C-R relations between exposure concentrations (C) and mortality rates (R).

In multivariate regression analyses, other explanatory variables in the date set (especially year, month of year (with the winter months of December-February being high-risk months as well as high-pollution months), and minimum temperature) are all highly statistically significant predictors of all-cause and cardiovascular disease mortality rates in different age categories. PM2.5, too, is a strong predictor of all-cause and CVD mortality rates. After conditioning on other variables, however, no positive statistical effect of PM2.5 on mortality rates remains. For example, Table 1 shows the results of a multiple linear regression model fit to the data (using the commercial statistical software environment *Statistica 9.0*. The *b* coefficients are the ordinary least squares regression coefficients, and the *b** coefficient are their standardized values. The variable *Dec-Feb* is a binary variable with value 1 for these three months and 0 for other months.) Both estimated PM2.5 exposure (*pm25Reconstruct*) and all-cause mortality rates are highest in the winter months: the variable Dec-Feb is a con-

TABLE 1. Multiple Linear Regression Model for All-Cause Mortality Rates in 10 Cities

Regression Summary for Dependent Variable: death (all causes) R= .41 R?= .17 Adjusted R?= .17						
N=22242	b*	Std.Err. of b*	b	Std.Err. of b	t(22235)	p-value
Dec-Feb	0.16	0.007	31.66	1.50	21.2	0.000000
tmin	0.15	0.008	0.83	0.04	20.0	0.000000
Year	0.02	0.006	0.35	0.14	2.6	0.009320
Month	-0.02	0.006	-0.47	0.16	-3.0	0.002524
pm25Reconstruct	-0.02	0.006	-0.18	0.05	-3.4	0.000589
pHisp	-0.43	0.007	-226.40	3.47	-65.3	0.000000
Intercept			-619.44	270.48	-2.3	0.022023

founder that explains a positive univariate association between them, as shown in Figure 1D. However, in the multivariate model in Table 1, the coefficient of PM2.5 exposure is significantly *negative*, suggesting that, apart from such confounding, PM2.5 exposure does not increase mortality rates. Although, any such ecological regression (with unknown individual exposures) must be interpreted with caution, it is noteworthy that the apparent positive association between PM2.5 and mortality in Figure 1D is entirely removed by controlling for other variables in multivariate analysis, leaving a negative association at sufficiently low exposure concentration (and hence hormesis, overall) as a viable possibility.

Table 2 shows analogous results specifically for CVD mortality rates. Although both all-cause and CVD mortality rates are significantly predicted by month of year, as well as year (as mortality rates fall and life expectancies rise over time), minimum temperature (tmin), and proportion of Hispanics in the population, it is conspicuous that PM2.5 (the *pm25reconstruct* variable) has no significant positive relation with either mortality rate. The same is true in non-linear (e.g., polynomial regression and classification tree) models with interaction effects, for lagged values of PM2.5, and for other health end points, including respiratory mortality rate: *PM2.5 at ambient levels is not significantly positively associated with any adverse health outcomes.* This observation for ten U.S. cities is generally consistent with the results of Koop and Tole (2004) for Toronto.

Although reports of mixed positive and negative associations of PM2.5 concentrations with mortality rates are common in the literature (Daniels *et al.* 2000, Franklin *et al.* 2007, Koop *et al.* 2007, Joseph 2008), and although they may suggest a possible U-shaped or J-shaped relation between exposure concentrations and mortality rates, epidemiological studies are generally too weak and ambiguous to decisively reveal the true shape of the concentration-response function. Principal reasons include the lack of reliable measurements of individual exposures and lack of complete identification and control of confounders, both of which cast

TABLE 2. Multiple Linear Regression Model for Cardiovascular Mortality Rate

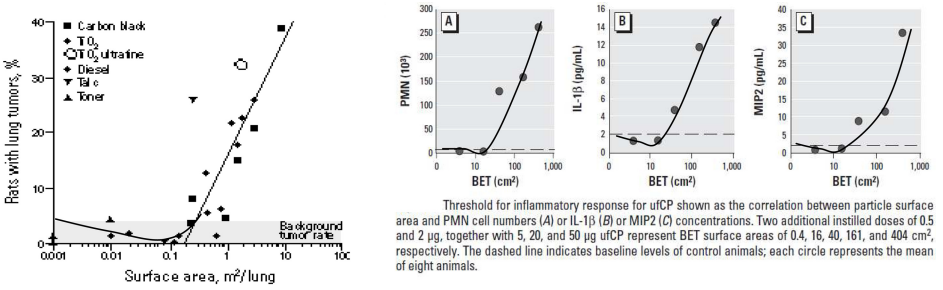
Regression Summary for Dependent Variable: cvd R= .37 R?= .14 Adjusted R?= .14						
N=22242	b*	Std.Err. of b*	b	Std.Err. of b	t(22235)	p-value
Dec-Feb	0.14	0.01	15.53	0.85	18.2	0.000000
tmin	0.12	0.01	0.36	0.02	15.0	0.000000
pm25Reconstruct	-0.01	0.01	-0.06	0.03	-1.8	0.068621
Month	-0.02	0.01	-0.22	0.09	-2.4	0.016366
Year	-0.05	0.01	-0.56	0.08	-7.3	0.000000
pHisp	-0.38	0.01	-110.64	1.98	-55.8	0.000000
Intercept			1170.99	154.60	7.6	0.000000

severe doubt on statistical estimates and inferences obtained by plugging estimated city-level exposures into regression or time series models as presumed explanatory variables (Sheppard *et al.* 2011). In addition, statistical associations (of any sign) need not necessarily reflect causality. Therefore, is desirable to consider toxicological dose-response data, to see whether a J-shaped relation is consistent with experimental data.

EXPERIMENTAL DATA SHOW J-SHAPED CONCENTRATION-RESPONSE RELATIONS

Experimental studies in human volunteers, including asthmatics, have led some commentators to conclude that, "[T]he weight of the evidence from controlled studies with animals and human volunteers suggests that PM is unlikely to cause premature death or other serious health effects at levels found in real-world air" (Schwartz 2007). This is consistent with earlier conclusions that, "It remains the case that no form of ambient PM — other than viruses, bacteria, and biochemical antigens — has been shown, experimentally or clinically, to cause disease or death at concentrations remotely close to US ambient levels" (Green and Armstrong 2003). To test such reassuring-looking conclusions more carefully, it is instructive to examine the concentration-response relations for particulate matter in animals, where concentrations have been varied systematically from low levels, at which no adverse effects are observed, to much higher levels at which inflammation in mice and rats, and fibrosis and lung tumors in rats, can be induced.

Figure 2 summarizes two sets of experimental data. The left panel shows lung tumor responses in rats (the only species that develops them) in response to varying concentrations of different types of particulates. The mechanism of tumor induction involves overwhelming of antioxidant and clearance defenses, unresolved chronic inflammation, repetitive injury to lung tissue, and fibrosis, scarring, and proliferation leading to tumors (Azad *et al.* 2008, Oberdörster 1997). The three right panels



Rat tumors (adapted from Oberdorster 1997) Mouse inflammation markers (adapted from Stoeger et al. 2006)

FIGURE 2. Rat tumor (left-most) and mouse inflammation (right) responses to PM. Original figures reproduced with permission from *Environmental Health Perspectives,* www.ncbi.nlm.nih.gov/pmc/articles/PMC1392224/figure/f3-ehp0114-000328/, doi: 10.1289/ehp.8266 and www.ncbi.nlm.nih.gov/pmc/articles/PMC1470142/?tool=pubmed. J-shaped curves have been superimposed on the original figures.

show the responses of three inflammatory markers in mice, to different concentrations of ultrafine carbon particulates (ufCP).

In both experiments, the surface area of particles in the lung is used as a dose metric, since it is the best predictor of response (better than mass or volume of PM. The "BET" protocol referred to on the right side provides a way to quantify this surface area.) The original authors of these experimental studies interpreted their findings as showing a threshold exposure level, below which exposure did not increase risk of adverse responses (inflammation in mice, on the right; tumors in rats, resulting from unresolved inflammation and associated other effects, on the left). However, as indicated by the J-shaped cuves that we have superimposed on the data points, the data are actually more consistent with hormesis, i.e., a positive baseline level at zero exposure that is reduced by very low levels of exposure, but that increases above background at higher exposure concentrations. Thus, while there may indeed be an exposure concentration level below which risk of adverse effects is not greater than background, it is more accurate to interpret the J-shaped curves as indicating hormesis, rather than thresholds.

DISCUSSION AND CONCLUSIONS

EPA's assumption that the concentration-response (C-R) function relating changes in ambient exposure concentrations of fine particulate matter (PM2.5) is well-described by a straight line with a positive slope (with 100% confidence, based on a subjective Weibull uncertainty analysis that precludes zero and negative slopes from having positive subjective probabilities), poses a direct challenge to the hypothesis of hormesis. We have reexamined empirical evidence on the shape of the C-R function, and find that such certainty that a positive linear C-R relation provides a

better description that alternative, hormetic (J-shaped) relations is unjustified. A J-shaped relation provides one possible explanation for common reports in the literature of statistically significant negative, as well as positive, C-R coefficients. However, in the absence of more accurate and detailed information about individual exposures, as opposed to ambient exposures at monitoring locations, epidemiological data alone cannot decisively establish the true shape of the C-R function (Sheppard *et al.* 2011). In our own analysis of a data set made available for public analysis, there is no clear positive relation between PM2.5 and all-cause or cause-specific mortality rates, although cause-specific mortality rates are significantly correlated with each other.

Turning to toxicological data, the results are clearer: in animal studies with accurate exposure measurements for individual animals, it is clear that inflammatory responses (and tumors in rat lungs) are not increased by sufficiently low exposures, contrary to the low-dose linear no-threshold assumption. As shown in Figure 2, hormesis (J-shaped dose-response relations) provides a description of such data.

In conclusion, available evidence supports the hypothesis of hormesis more strongly than the hypothesis of a positive linear no-threshold model for PM2.5 and mortality risks. Experimental evidence (Figure 2) indicates hormesis as the hypothesis that best fits the data. Epidemiological data, although more ambiguous (Figure 1), is consistent with hormesis in meta-analyses, as evidenced by mixed positive and negative C-R coefficients.

However, it is not necessary to settle conclusively whether hormesis holds for PM2.5 in order for it to have major policy implications. Recent EPA estimates of the human health benefits from the 1990 Clean Air Act Amendment (EPA, 2011) are crucially dependent on the unverified assumption of a positive linear no-threshold C-R function for PM2.5. As soon as it is acknowledged that hormesis is at least a plausible possibility – so that assigning it a subjective probability of zero, as in EPA's benefit assessment, is not warranted by data – it follows that the true incremental human health benefits of the 1990 Clean Air Act Amendment could also be zero or negative in many locations. This changes the nature of the cost-benefit comparison presented to the public from an apparent certainty of large positive return, in which compliance costs of $65 billion per year are said to produce lower mortality risks among the elderly, valued by EPA at about two trillion dollars per year, to a revised comparison in which the expenditure of $65 billion per year in compliance costs may instead – with probability of greater than 50%, if hormesis is more plausible than low-dose linearity – produce zero or negative net health benefits in reducing mortality risks. Many policy-makers who would embrace the former description might reject the latter, or at least request much more information about the uncertainties and evidence on the shape of the C-R function for PM2.5 at and below current ambient levels.

Thus, the hypothesis of hormesis, which appears to be supported by experimental data and consistent with (but not decisively proved or refuted by) current epidemiological data, changes the policy evaluation of claimed marginal health benefits of the 1990 Clean Air Act Amendment from a clear win for the public to a possible loss. More careful evaluation of the true shape of the C-R function is needed to determine which is correct. However, that the hypothesis of hormesis is plausible for a major air pollutant such as PM2.5 already provides sufficient grounds to question regulatory benefits assessments, evaluations, and policies that assume that cleaner air necessarily reduces mortality risks, even at and below current ambient concentrations.

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